Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

A Comparison of the Effect of Remimazolam and Midazolam on Recovery and Preserved Memory Function for Patients with Dental Extraction Anxiety

Quan Jing[1,*], Weijia Wang[2,*], Limeng Wu[1], Lejunzi Wang[2], Boru Yuan[2], Yan Wang[2], Chengbin Wang[3], Lin Liu[4], Lei Guan[5], Riyue Yu[6], Yuelun Zhang[7], Daniel I Sessler[8,9], Yuguang Huang[2], Kuo Wan[1], Lijian Pei[2]

[1]Department of Stomatology, Peking Union Medical College Hospital, Beijing, People's Republic of China; [2]Department of Anesthesiology, Peking Union Medical College Hospital, Beijing, People's Republic of China; [3]Department of Anesthesiology, Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China; [4]Department of Stomatology, Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China; [5]Department of Anesthesiology, Beijing You'an Hospital, Capital Medical University, Beijing, People's Republic of China; [6]Department of Stomatology, Beijing Shijitan Hospital, Capital Medical University, Beijing, People's Republic of China; [7]Medical Research Center, Peking Union Medical College Hospital, Beijing, People's Republic of China; [8]Center for Outcomes Research and Department of Anesthesiology, UTHealth, Houston, TX, USA; [9]Outcomes Research Consortium®, Houston, TX, USA

*These authors contributed equally to this work

Correspondence: Lijian Pei, Department of Anesthesiology, Peking Union Medical College Hospital, Dongdan District, No. 1, Shuaifuyuan, Beijing, 100730, People's Republic of China, Tel +86 18612672127, Fax +86 10 69155581, Email hazelbeijing@vip.163.com; Kuo Wan, Department of Stomatology, Peking Union Medical College Hospital, Dongdan District, No. 1, Shuaifuyuan, Beijing, 100730, People's Republic of China, Tel +86 15811185513, Email wankuo@126.com

Purpose: Remimazolam is an ultrashort-acting benzodiazepine, which has been indicated to be effective in endoscopic surgery and general anaesthesia. Research on its use in outpatient dental procedures remains limited. This triple-blinded randomized clinical trial was designed to determine whether the quality of postoperative recovery is better with continuous intravenous remimazolam administration compared with midazolam administration for impacted wisdom tooth extraction in patients with dental anxiety.

Patients and Methods: This study was a randomized, parallel triple-blinded, superiority trial conducted between 30 April 2022 and 24 June 2024. Participants aged ≥18 years who exhibited dental anxiety and who were eligible for impacted wisdom tooth extraction in an outpatient setting were included in this study. Participants were randomly assigned at a 1:1 ratio to receive either a continuous intravenous infusion of remimazolam or midazolam. The primary outcome was the time to recover full alertness. The secondary outcome was postoperative anterograde amnesia.

Results: A total of 150 participants were randomized in this study, with 75 patients assigned to the remimazolam group and 75 patients assigned to the midazolam group. The time to complete alertness was significantly shorter in the remimazolam group than in the midazolam group (3.0 ± 3.6 min vs 4.7 ± 5.2 min, mean difference, −1.9 min; 95% CI, −3.3min to −0.4 min; P = 0.013). The odds of immediate and delayed anterograde amnesia were much reduced with remimazolam administration compared with midazolam administration (immediate: 0.14, 95% CI, 0.05 to 0.34, delayed: 0.07, 95% CI, 0.03 to 0.15, both P < 0.001).

Conclusion: For patients with dental anxiety, remimazolam offers not only faster recovery, but also a much better restoration of memory function compared with midazolam.

Trial Registration: https://clinicaltrials.gov/study/NCT05350085.

Plain Language Summary:

This study compared the effects of two sedatives—remimazolam (an ultrashort-acting benzodiazepine) and midazolam—in 150 outpatients with dental anxiety undergoing wisdom tooth extraction. In this randomized, triple-blinded trial, patients received either continuous intravenous remimazolam (n = 75) or midazolam (n = 75). The results showed that remimazolam not only led to significantly faster

Received: 4 July 2025
Accepted: 10 December 2025
Published: 30 December 2025

recovery (3.0 ± 3.6 min vs 4.7 ± 5.2 min to full alertness, p = 0.013) but also substantially reduced both immediate and delayed anterograde amnesia (p < 0.001) compared to midazolam. In other words, postoperative memory function—whether immediate or delayed—was better preserved with remimazolam. These findings suggest that remimazolam offers quicker recovery and fewer memory disturbances for outpatients, making it a superior choice for outpatient sedation procedures.

Keywords: antegrade amnesia, benzodiazepine, outpatient surgery, procedure sedation, remimazolam, besylate

Introduction

Dental anxiety is a common emotional reaction that leads to the avoidance of dental treatment and has a major impact on both oral and general health.[1] For these patients, tooth extraction often needs to be performed under intravenous sedation in an outpatient setting.[1–3] Given the increasing demand for same-day dental procedures, achieving faster and more effective recovery is crucial. In most cases, either propofol or an opioid is administered intravenously, and occasionally, a combination of both is used. While these agents can quickly induce sedation and provide analgesic effects, they may also result in excessive sedation or respiratory depression. Invasive dental procedures in the outpatient setting have unique requirements: patients must remain responsive to verbal and tactile cues during the procedure, and they need to rapidly regain full alertness and the ability to independently complete essential tasks, such as paying medical bills and memorizing and following the physician's instructions.

For conscious sedation, benzodiazepines such as midazolam have distinct advantages.[1,3] However, midazolam's longer induction and recovery times, along with its tendency to induce antegrade amnesia, present challenges.[4] In contrast, remimazolam is an ultrashort-acting benzodiazepine with a short half-life, resulting in a rapid onset of action, minimal respiratory and circulatory effects, and lower rates of adverse reactions, making it a promising option for clinical application.[5,6] While its efficacy in endoscopic surgery[7,8] and general anaesthesia[9,10] has been established, research on its use in invasive dental procedures in the outpatient clinical setting remains limited. Furthermore, evidence regarding remimazolam's impact on postoperative memory function remains scarce.

Therefore, we conducted a multicentre randomized controlled trial (RCT) to compare remimazolam and midazolam in terms of the postoperative recovery time, anterograde amnesia, and safety in patients with dental anxiety undergoing impacted wisdom tooth extraction in an outpatient setting.

Materials and Methods

Study Design and Setting

This multicentre, randomized, triple-blind, superiority trial with two parallel arms was conducted in three tertiary care hospitals. This study complied with the Declaration of Helsinki, which was approved by the Ethics Review Committees of the Peking Union Medical College Hospital (approval number: ZS-3142) and the other participating centres, including the Beijing Anzhen Hospital (approval number: KS2022082) and Beijing Shijitan Hospital (approval number: 2023–4). The study rationale and methodology have been published elsewhere.[11] Written informed consent was obtained from each participant. The trial is reported according to the Consolidated Standards of Reporting Trials guidelines.

Study Population

Potential participants were screened using the Modified Dental Anxiety Scale (MDAS) at the outpatient clinic.[12] This scale is a patient-reported questionnaire comprising five items that are designed to assess dental anxiety. The total score, calculated as the sum of responses to all items, ranges from 5 to 25. A score of 5 indicates no anxiety, while a score of 25 reflects the most severe dental anxiety, with higher scores denoting greater severity of anxiety. The Chinese version of the MDAS has been validated.

We enrolled individuals aged 18 years and older with MDAS scores > 15 who were scheduled for extraction of impacted mandibular wisdom teeth. We excluded those who were pregnant, experienced respiratory infections, had asthma attacks or persistent conditions, suffered from severe cardiopulmonary or hepatorenal insufficiency, had neuromuscular or mental disorders affecting communication or informed consent, had known allergies or contraindications to benzodiazepines, or had participated in other drug trials within the past 6 months.

Randomization

Participants were randomly assigned to treatment groups using a 1:1 allocation ratio. An independent biostatistician generated the randomization sequence using SAS software (SAS Institute, Cary, NC), ensuring stratification by trial site. The randomization employed variable block sizes ranging from 4 to 8 to maintain allocation concealment and balance between groups.

The block sizes were randomly determined and varied throughout the trial, with each block containing an equal number of assignments to each treatment group. Allocations were sealed in sequentially numbered opaque envelopes controlled by investigators who were not involved in recruitment, data acquisition, or participant care. The participants received either 25 mg of remimazolam or 15 mg of midazolam diluted in 50 mL of normal saline. Syringes that were labelled "trial drugs" were then provided to the anaesthesiologists for mandibular impacted wisdom teeth extraction. All of the participants, anaesthesiologists, dental surgeons and outcome assessors were blinded to the group assignments, with unblinding being permitted only in emergencies.

Procedures and Intervention

Patient monitoring methods included electrocardiography, noninvasive blood pressure, and pulse oximetry, with measurements taken every 5 minutes. The standard procedural sedation protocol was as follows:

(1) Induction phase: The first dose was administered via a mini-syringe pump at 100 mL/hour, with participants observed until they reached Ramsay Sedation Grade III.[13]
(2) Maintenance phase: During this phase, the pump rate was maintained at 10–30 mL/hour and adjusted accordingly until the participants reached Ramsay sedation grade III and had a Houpt score ≥ 5.
(3) Cessation phase: The microinjection pump was stopped five minutes after the procedure if there was no active bleeding.

Advanced local anaesthesia procedures (ALAPs; see Appendix Video 1) were performed after induction and before the invasive procedure was conducted. First, the buccal mucosa was dried, topical lidocaine was applied at the injection site, and saliva was controlled with a cotton ball for 2 minutes. Second, a pathway for the anaesthetic was established by injecting 4% articaine with epinephrine into the submucosa via a single-tooth anaesthesia system. Finally, 2% lidocaine was injected for inferior alveolar, lingual, and long buccal nerve blocks.

Failure to achieve Ramsay sedation grade III after more than 50 mL of medication administration was considered to indicate sedation failure; if sedation failed, surgery was resumed under general anaesthesia.

After discontinuation, the patient's condition was assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale every minute until the MOAA/S score was 5 three consecutive times.[14] A score of 5 indicates full alertness, with a response to normal tone, while a score of 0 reflects no response to a painful stimulus. Intermediate scores represent decreasing levels of responsiveness: 4 for lethargic response to normal tone, 3 for response to loud/repeated calling, 2 for response to mild prodding, and 1 for response to a painful squeeze. Participants who did not achieve a MOAA/S score of 5 within 20 minutes after discontinuation of the infusion received 0.3 mg flumazenil as an antagonist. The participants were then transferred to the postanaesthesia care unit and discharged after achieving an Aldrete score ≥ 9.

Data Collection and Follow-up

Outcomes and Data Collection

The primary outcome was the time to regain complete alertness, defined as the time from the discontinuation of the sedative injection to the time at which the MOAA/S score was 5 three consecutive times.

The secondary outcome was restoration of postoperative memory formation evaluated with anterograde amnesia. The participants viewed three cards with different images during recovery and were asked to recall them immediately and again five minutes later. Failure to recall all three images indicated anterograde amnesia. The observation time points for

immediate anterograde amnesia were 0, 15, and 30 min after complete alertness, and the observation time points for delayed anterograde amnesia were 5, 20, and 35 min after complete alertness.[15]

The exploratory outcomes included dizziness and resleeping one hour after full alertness, and the postoperative MDAS scores were collected 30 days after treatment via telephone follow-up. Adverse events, procedure duration, and drug dosage were also recorded. All the data were documented in the case report form (CRF).

Statistical Analysis

Statistical analyses were performed using the intention-to-treat population, which comprised the participants who were randomized. The patients' baseline and intraoperative factors were described. The absolute standardized difference (ASD) was used to evaluate for potential imbalanced baseline factors, and these imbalanced factors (ASD $\geq$ 0.2; Cohen's d effect size) were further adjusted for in multivariable models.

The primary outcome values were compared between the treatment groups by using a linear regression model. For secondary analysis, we treated the primary outcome as a time-to-event variable and analysed it by using a Cox proportional hazards model. If there were missing data for the primary outcome, we applied the most conservative approach to handle missing data by imputing the longest observed time to complete alertness (worst-case scenario) for the remimazolam group and the shortest observed time to complete alertness (best-case scenario) for the midazolam group. We also conducted a sensitivity analysis with a complete case dataset by excluding those who had missing primary outcome data. We reported the results from both the univariable analysis and the multivariable analysis, in which imbalanced preoperative factors and research centres were adjusted. We evaluated possible treatment effect heterogeneity across the centres by testing treatment-by-centre interaction terms in all of the models.

For the secondary outcomes, we assessed overall anterograde amnesia at multiple post-alertness time points (defined as any observed sign or symptom of amnesia) by using generalized estimating equation (GEE) logistic regression with unstructured correlation and adjusting for the imbalanced preoperative factors and research centres. We first tested for treatment effect heterogeneity across time points by evaluating the treatment-by-time interaction (significance threshold: $P < 0.05$). When this interaction was not statistically significant, we collapsed the data across time points to assess the overall treatment effect on the secondary outcomes (main effects GEE model). We also compared any occurrence of anterograde amnesia during observation by using multivariable logistic regression and adjusting for the baseline preoperative MDAS scores and research centres.

Exploratory outcomes were analyzed using descriptive statistics. We calculated percentages, means, and standard deviations (SD) for relevant variables. No formal statistical tests were conducted for these exploratory outcomes, as the focus was on providing an initial understanding of the data patterns.

The mean difference (MD), odds ratio (OR), and hazard ratio (HR) with 95% confidence interval (CI) were used as effect size measures for continuous, binary, and time–to-event outcomes, respectively. A two-sided P value <0.05 indicated statistical significance.

Sample Size Considerations

Previous studies revealed that the standard deviation of the time to complete alertness was approximately 8.7 min (SD = 5.78 min in remimazolam, SD = 11.57 min in midazolam).[5] Assuming a two-sided α of 0.05 and accounting for a 10% dropout rate, a total of 150 patients (75 per group) will provide 80% power to detect a clinically meaningful between-group difference of 4 minutes.

Statistical analyses were performed by using R (version 4.4.1; R Foundation, Vienna, Austria; www.r-project.org).

Results

Study Participants

A total of 150 patients participated in the study between April 30, 2022, and June 24, 2024. Among these, 75 patients were randomized to the remimazolam group, and 75 were randomized to the midazolam group (Figure 1). The sedation success rates were 97.3% (73 patients) for remimazolam and 98.7% (74 patients) for midazolam. Two patients in the remimazolam group and one patient in the midazolam group had sedation failure. These three patients were included in

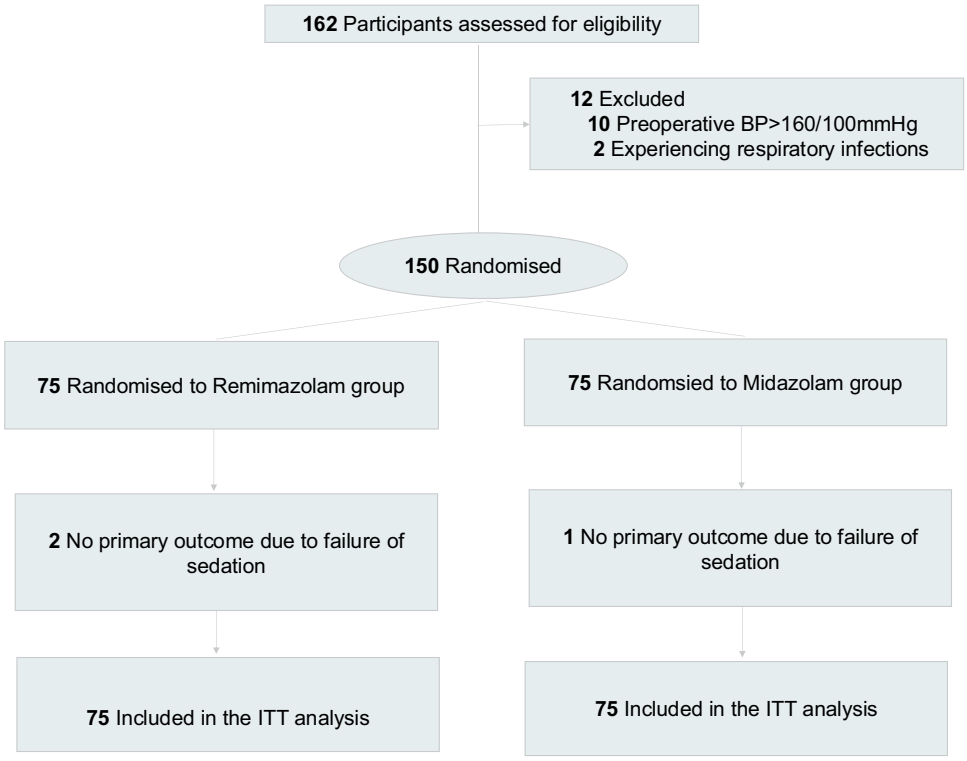

Figure 1 Study flowchart: remimazolam vs midazolam for tooth extraction.

the ITT analysis. However, due to sedation failure, they did not have measurements for the primary outcome. In the primary analysis, the missing time to complete alertness for the two patients in the intervention group was imputed with the worst observed value among all patients, 22 minutes. For one patient in the control group, the missing time to complete alertness was imputed with the best observed value, 1 minute. This represents the most conservative assumption for conducting the ITT analysis. Eighteen and fourteen patients were lost to follow-up at 30 days in the remimazolam and midazolam groups, respectively. The baseline variables were similar between the two groups, except for the preoperative MDAS scores and research centre allocation (Table 1). The preoperative MDAS scores were 20 and 18

Table 1 Baseline and Intraoperative Factors of the Patients (ITT Population, N = 150)

Factors[a]	Remimazolam N = 75	Midazolam N = 75	ASD[b]
Baseline factors			
Research centre			0.13
1	38 (50.7)	34 (45.3)	
2	17 (22.7)	17 (22.7)	
3	20 (26.7)	24 (32.0)	
Age, y	31.3 ± 8.8	31.8 ± 7.9	0.07
Height, cm	167.9 ± 7.5	167.1 ± 7.0	0.12
Weight, kg	62.5 ± 12.5	61.9 ± 11.7	0.05
BMI, kg/cm^2	22.0 ± 3.1	22.0 ± 3.1	0.01

(*Continued*)

https://doi.org/10.2147/DDDT.S551322

Table 1 (Continued).

Factors[a]	Remimazolam N = 75	Midazolam N = 75	ASD[b]
Sex			0.15
Male	23 (30.7)	18 (24.0)	
Female	52 (69.3)	57 (76.0)	
ASA classification			0.06
I	56 (74.7)	54 (72.0)	
2	19 (25.3)	21 (28.0)	
Preoperative sleep medication use	0 (0)	0 (0)	0.00
Preoperative MDAS score	20.0 (17.0–21.5)	18.0 (16.0–21.0)	0.26
Procedure time, min	36.8 ± 15.0	37.7 ± 16.6	0.06
Intraoperative factors			
Induction time, min	5.44 ± 1.27	5.84 ± 1.74	–
Induction dose, mg kg^{-1}	0.07 ± 0.03[c]	0.05 ± 0.02[d]	–
Total dose of medicine, mg kg^{-1}	0.24 ± 0.10[c]	0.14 ± 0.05[d]	–
Successful sedation	73 (97.3)	74 (98.7)	–
Houpt behaviour scale	6 (6–6)	6 (6–6)	–
Coughing causes procedural interruption	4 (5.3)	2 (2.7)	–
Use of flumazenil	0 (0)	4 (5.3)	–

Notes: [a]Continuous factors are presented as mean ± SD or median (IQR). Categorical factors are presented as n (%). [b]Factors with an ASD ≥ 0.20 were regarded as imbalanced between the groups and were adjusted for in the primary analysis. The ASD for intraoperative factors was not calculated because it was highly influenced by the intervention. [c]Two patients with missing data due to sedation failure. [d]One patient with missing data due to sedation failure.

Abbreviations: ASA, American society of anesthesiologists; ASD, absolute standardized difference; BMI, body mass index; IQR, interquartile range; ITT, intention-to-treat; MDAS, modified dental anxiety scale; NA, not applicable; SD, standard deviation.

in the remimazolam and midazolam groups, respectively; these patients were diagnosed with dental phobia (MDAS score ≥15). None of the participants in either group used sleep medications or benzodiazepine.

The induction times of remimazolam and midazolam were 5.44±1.27 minutes and 5.84±1.74 minutes, respectively, with doses of 0.07±0.03 mg/kg and 0.05±0.02 mg/kg, respectively. The total surgery durations were similar between the groups, while the total drug dosages were 0.24±0.10 mg/kg for remimazolam and 0.14±0.05 mg/kg for midazolam. The incidence of transient coughing causing interruptions was 5.33% (4 patients) in the remimazolam group and 2.67% (2 patients) in the midazolam group.

Primary Outcome

The primary outcome (which was adjusted for the imbalanced preoperative MDAS scores and research centres) indicated that the time to regain full alertness was significantly shorter in the remimazolam group (3.0 ± 3.6 min) than in the midazolam group (4.7 ± 5.2 min) (mean difference, −1.9 min; 95% CI, −3.3 to −0.4 min; P = 0.013; Table 2 and Figure 2). On average, patients in the remimazolam group regained full alertness 1.9 minutes faster than those in the midazolam group. The time to alertness was significantly shorter with remimazolam versus midazolam (adjusted HR=1.6; 95% CI: 1.1–2.2; P <0.001), which implied that at any given point in time, patients in the remimazolam

Table 2 Comparison of the Time to Complete Alertness (ITT Population, N = 150)[a]

Primary Outcome	Remimazolam (N = 75)	Midazolam (N = 75)	Univariable analysis		Multivariable Analysis[b]	
Time to complete alertness (min)			**Effect size (95% CI)**	**P value**	**Effect size (95% CI)**	**P value**
Primary analysis: as a continuous variable	3.0 ± 3.6[c]	4.7 ± 5.2[c]	−1.8 (−3.2–−0.3)[d]	0.016	−1.9 (−3.3–−0.4)[d]	0.013
Secondary analysis: as a time-to-event variable	2.0 (1.0–3.0)[e]	3.0 (1.0–5.5)[e]	1.5 (1.1–2.1)[f]	0.012	1.6 (1.1–2.2)[f]	0.010

Notes: [a]Two and one patients with sedation failure were observed in the remimazolam and midazolam groups, respectively. These three patients were included in the ITT analysis. However, due to sedation failure, they did not have measurements for the primary outcome, the time to regain complete alertness. In the primary analysis, the missing time to regain complete alertness for the two patients in the intervention group was imputed with the worst observed value among all patients, 22 minutes. For one patient in the control group, the missing time to regain complete alertness was imputed with the best observed value, 1 minute. This represents the most conservative assumption for conducting the ITT analysis. [b]Adjusted for the imbalanced preoperative MDAS scores and research centres, as evaluated by the absolute standardized difference in Table 1. No statistically significant interaction effect between treatment effect and research centre was observed in any of the multivariable models. [c]Presented as the mean ± SD. [d]Mean difference. [e]Median (IQR). [f]Hazard ratio.
Abbreviations: CI, confidence interval; IQR, interquartile range; SD, standard deviation.

group were 1.6 times more likely to regain alertness compared to those in the midazolam group. The sensitivity analysis with complete case data yielded consistent results. Tests for heterogeneity of the treatment effect across the centres were nonsignificant in all of the adjusted models (all P values > 0.05). Notably, none of the patients in the remimazolam group required flumazenil, whereas four patients in the midazolam group necessitated flumazenil due to delayed recovery of consciousness. No adverse events were observed in either group.

Secondary Outcomes

Table 3 and Figure 3 present the immediate and delayed anterograde amnesia in both groups. Compared with the midazolam group, the remimazolam group presented significantly lower odds of anterograde amnesia. For immediate anterograde amnesia, the OR was 0.14 (95% CI, 0.05 to 0.34; P < 0.001). Similarly, for delayed anterograde amnesia, the OR was 0.07 (95% CI, 0.03 to 0.15; P < 0.001). Additionally, for overall anterograde amnesia, the results indicated that

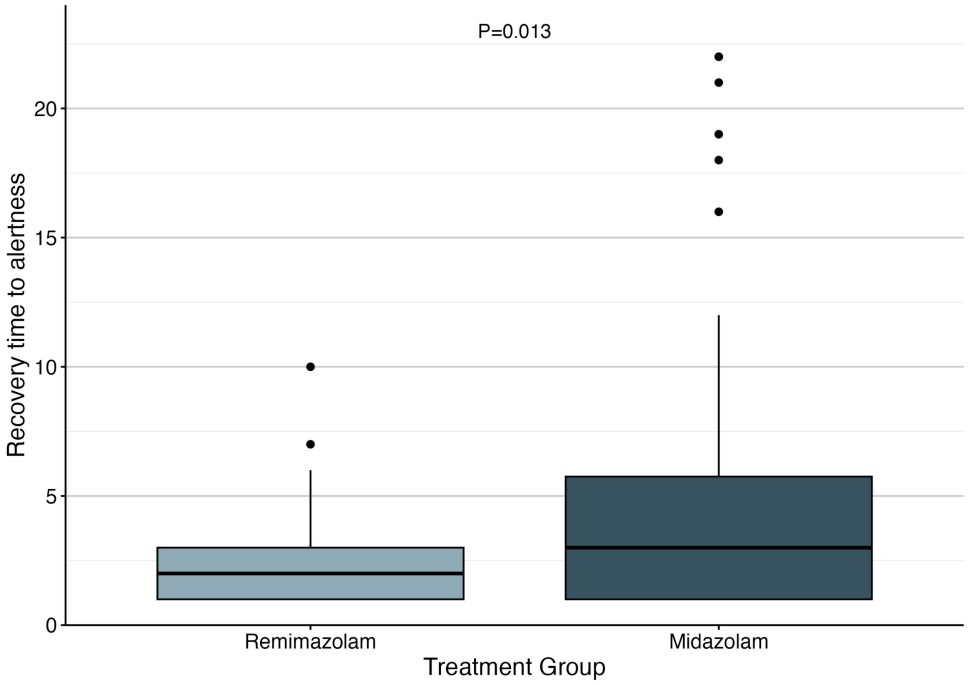

Figure 2 Comparison of the recovery times between the remimazolam and midazolam groups by using a linear regression model adjusted for the imbalanced preoperative MDAS scores and research centres. The data showed that remimazolam treatment significantly reduced recovery time (adjusted p = 0.013).

https://doi.org/10.2147/DDDT.S551322

Table 3 Comparison of Secondary Outcomes (ITT Population, N = 150)

Anterograde Amnesia at Different Time Points After Regaining Complete Alertness	Remimazolam, n (%) (N = 75)	Midazolam, n (%) (N = 75)	Odds Ratio (95% CI)[a]	P value[a]
Immediate anterograde amnesia				
Treatment×time interaction GEE model				0.430[b]
Main effect GEE model			0.14 (0.05–0.34)	< 0.001
0 (min)	3 (4.0)	19 (25.3)		
15 (min)	6 (8.0)	23 (30.7)		
30 (min)	6 (8.0)	19 (25.3)		
Any immediate anterograde amnesia	9 (12.0)[c]	29 (38.7)[c]	0.15 (0.05–0.40)[c]	< 0.001
Delayed anterograde amnesia				
Treatment×time interaction GEE model				0.860[b]
Main effect GEE model			0.07 (0.03–0.15)	< 0.001
5 (min)	23 (30.7)	63 (84.0)		
20 (min)	9 (12.0)	48 (64.0)		
35 (min)	5 (6.7)	33 (44.0)		
Any delayed anterograde amnesia	23 (30.7)[c]	64 (85.3)[c]	0.06 (0.02–0.14)[c]	< 0.001

Notes: [a]Estimated from a generalized estimating equation (GEE) logistic regression model adjusted for imbalanced baseline MDAS scores and research centres. The time to regain complete alertness was defined as the time from the discontinuation of sedative injection to the time at which the MOAA/S score was 5 three consecutive times. Anterograde amnesia was defined as the patient's inability to recall the three cards at the time of assessment. An exchangeable correlation structure was used in the model. [b]P value for the interaction between treatment allocation and categorical time points in the GEE model. [c]Overall anterograde amnesia (defined as any sign or symptom of amnesia during observation) was regressed against treatment allocation, adjusting for baseline preoperative MDAS scores and research centres via logistic regression. This was the estimated odds ratio, 95% CI, and P value from the logistic regression model.

Abbreviations: CI, confidence interval; ITT, intention-to-treat.

the remimazolam group had significantly lower odds of both immediate anterograde amnesia (12.0% [9/75] vs 38.7% [29/75]; OR 0.15; 95% CI, 0.05 to 0.40; P < 0.001) and delayed anterograde amnesia (30.7% [23/75] vs 85.3% [64/75]; OR 0.06; 95% CI, 0.02 to 0.14; P < 0.001). These odds ratios highlighted the much reduced risk of amnesia associated

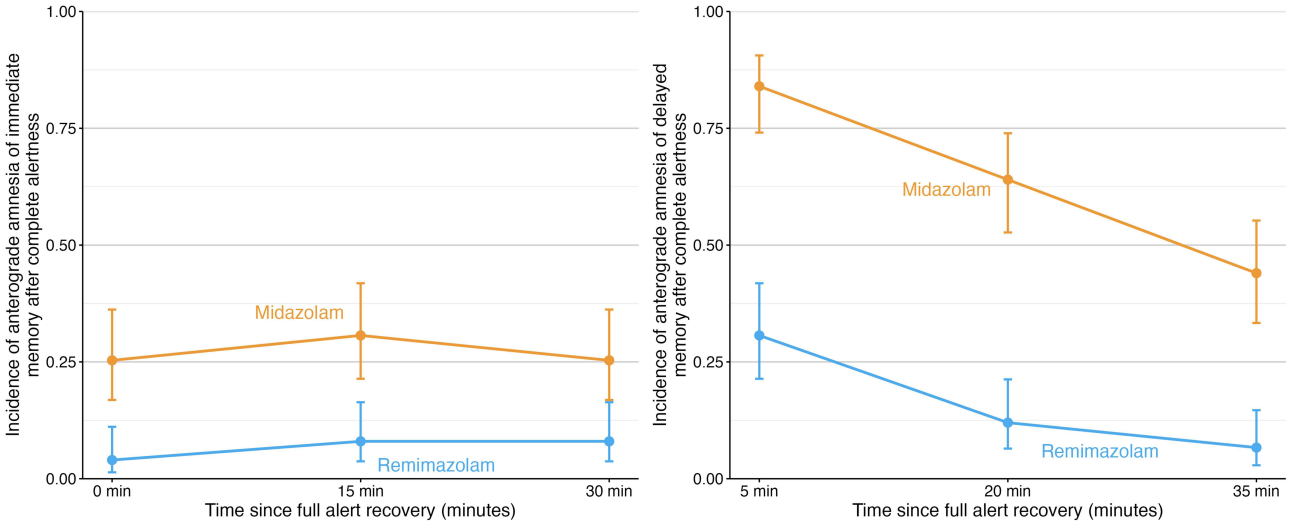

Figure 3 Temporal trends in anterograde amnesia after regaining complete alertness in the remimazolam and midazolam groups. Error bars represent the 95% confidence interval of the odds ratio.

with remimazolam, indicating a quicker return to normal memory function after the procedure. Tests for heterogeneity of the treatment effect across the time points were nonsignificant in all models (all $P > 0.5$).

Exploratory Outcomes

The incidences of postoperative dizziness and resleeping were lower in the remimazolam group than in the midazolam group (1.3% [1/75] vs 10.7% [8/75]). Additionally, both groups demonstrated a significant reduction in dental anxiety, as measured by the MDAS scores, at 30 days postoperatively. The MDAS scores decreased by 11.1 ± 4.7 in the remimazolam group and by 10.3 ± 5.4 in the midazolam group.

No adverse events were observed in either group.

Discussion

Our study revealed that compared with midazolam, remimazolam significantly accelerated the recovery of full alertness with less complication and markedly reduced the odds of immediate and delayed anterograde amnesia in patients with dental anxiety. The superior preservation of memory function observed with remimazolam suggests its potential advantage for outpatient sedation procedures. Besides, both drugs effectively provided sedation for patients with dental anxiety.

Invasive dental procedures in the outpatient setting present unique demands.[16] Patients must remain responsive to verbal and tactile cues during the procedure while achieving rapid recovery of full alertness and the ability to resume normal work and daily activities. Additionally, minimizing postoperative complications, such as respiratory or circulatory depression, is also crucial in outpatient care. The efficacy of remimazolam for procedural sedation has been previously demonstrated in three randomized, double-blind, multicentre Phase III trials involving colonoscopy and bronchoscopy patients.[7,8,17] In our study, we further confirmed that compared with midazolam, remimazolam was associated with a faster recovery, fewer complications, and reduced flumazenil requirements.[18,19]

Notably, although postoperative memory restoration - assessed by anterograde amnesia - was a secondary outcome, these findings demonstrate clinically meaningful effects with important practical implications. Anterograde amnesia (defined as the inability to form new memories after its onset) is a well-known memory disturbance associated with benzodiazepines.[20,21] However, few studies have quantitatively assessed its extent in outpatient procedures, particularly in dental settings where patients are expected to independently manage their postoperative care.[22,23] In this study, we systematically and quantitatively evaluated anterograde amnesia (both immediate and delayed types) and observed that patients receiving remimazolam exhibited substantially lower incidence rates of amnesia compared to those receiving midazolam, with a 66–95% reduction in immediate amnesia and an 85–97% reduction in delayed amnesia being detected. These findings suggest a more favourable cognitive recovery profile for remimazolam, with important practical implications being demonstrated. The preservation of memory function facilitates better understanding and adherence to postoperative instructions, thereby potentially reducing complications and enhancing recovery. Patients with intact recall are also more capable of performing self-care tasks and resuming normal activities, which are particularly valuable characteristics in outpatient care models that emphasise rapid turnover and patient autonomy. Consequently, the reduced odds of anterograde amnesia that were associated with remimazolam contributed to a positive treatment experience,[24] diminishing the fear of dental procedures. This finding was further supported by the observed postoperative reduction in dental anxiety. Given the strong association between anxiety and dental visits, helping patients manage their anxiety will also help them improve their oral health, and future research could explore the long-term effects of remimazolam on dental anxiety.[2,25,26]

Limitations of This Study

An important limitation of our study is that we focused exclusively on patients with dental anxiety who were undergoing impacted wisdom tooth extraction. This narrow scope may limit the generalizability of our findings to other invasive dental procedures. It also explains why nitrous oxide (N_2O) was not included in our study. Although N_2O is a common alternative in dental practice, intravenous sedation is more frequently used for patients with significant dental anxiety undergoing tooth extraction.[3] Furthermore, the distinctive effects of nitrous oxide make it difficult to conduct blinded studies when comparing it with benzodiazepines. Additionally, the dosage and duration of the intervention were determined on the basis of preclinical experiments and clinical practice, and we excluded individuals who were pregnant

or had severe cardiopulmonary or hepatorenal insufficiency, as these conditions can affect the metabolism of remimazolam. This approach may not fully account for variations in patient response, highlighting the need for further exploration to determine appropriate dosages for such patients during procedural sedation.

Conclusions

In this multicentre, randomized, triple-blinded superiority trial, our findings indicated that remimazolam significantly outperformed midazolam in enhancing the quality of recovery and reducing anterograde amnesia in patients with dental anxiety undergoing tooth extraction. These cognitive benefits, particularly the preservation of memory function, extend beyond remimazolam's established pharmacokinetic properties and offer a significant advantage. The findings suggest that remimazolam is a superior choice for dental outpatient procedures, where rapid recovery, cognitive clarity, and patient cooperation are crucial for effective treatment.

Abbreviations

MDAS, Modified Dental Anxiety Scale; ALAPs, Advanced local anaesthesia procedures; MOAA/S, Modified Observer's Assessment of Alertness/Sedation.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author, Dr. Lijian Pei, upon request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Review Committees of the Peking Union Medical College Hospital (approval number: ZS-3142) and the other participating centres, including the Beijing Anzhen Hospital (approval number: KS2022082) and Beijing Shijitan Hospital (approval number: 2023-4). Written informed consent was obtained from each participant.

Consent for Publication

Written informed consent was obtained from all individual participants included in the study for publication of the collected data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was sponsored by the National High Level Hospital Clinical Research Funding (No. 2022-PUMCH-B-035) and Peking Union Medical College Hospital Anesthesia Investigator-Initiated Trial (No.PUMCHAIIT-2025-05).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Hoffmann B, Erwood K, Ncomanzi S, Fischer V, O'Brien D, Lee A. Management strategies for adult patients with dental anxiety in the dental clinic: a systematic review. *Aust Dent J*. 2022;67(Suppl 1):S3–S13. doi:10.1111/adj.12926
2. Armfield JM, Heaton LJ. Management of fear and anxiety in the dental clinic: a review. *Aust Dent J*. 2013;58(4):390–407;quiz531. doi:10.1111/adj.12118

3. Melini M, Forni A, Cavallin F, Parotto M, Zanette G. Conscious sedation for the management of dental anxiety in third molar extraction surgery: a systematic review. *BMC Oral Health*. 2020;20(1):155. doi:10.1186/s12903-020-01136-0
4. Kim SH, Fechner J. Remimazolam - current knowledge on a new intravenous benzodiazepine anesthetic agent. *Korean J Anesthesiol*. 2022;75(4):307–315. doi:10.4097/kja.22297
5. Oka S, Satomi H, Sekino R, et al. Sedation outcomes for remimazolam, a new benzodiazepine. *J Oral Sci*. 2021;63(3):209–211. doi:10.2334/josnusd.21-0051
6. Lee A, Shirley M. Remimazolam: a review in procedural sedation. *Drugs*. 2021;81(10):1193–1201. doi:10.1007/s40265-021-01544-8
7. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427–437.e6. doi:10.1016/j.gie.2018.04.2351
8. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. *Chest*. 2019;155(1):137–146. doi:10.1016/j.chest.2018.09.015
9. Lohmer LL, Schippers F, Petersen KU, Stoehr T, Schmith VD. Time-to-event modeling for remimazolam for the indication of induction and maintenance of general anesthesia. *J Clin Pharmacol*. 2020;60(4):505–514. doi:10.1002/jcph.1552
10. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J Anesth*. 2020;34(4):543–553. doi:10.1007/s00540-020-02788-6
11. Wang L, Jing Q, Pei L, et al. Efficacy of continuous intravenous remimazolam versus midazolam in the extraction of impacted wisdom teeth: protocol of a randomised controlled trial. *BMJ Open*. 2023;13(4):e067908. doi:10.1136/bmjopen-2022-067908
12. Humphris GM, Morrison T, Lindsay SJ. The modified dental anxiety scale: validation and United Kingdom norms. *Community Dent Health*. 1995;12(3):143–150.
13. Van Dishoeck AM, Van Der Hooft T, Simoons ML, Van Der Ent M, Reimer WJSO. Reliable assessment of sedation level in routine clinical practice by adding an instruction to the Ramsay scale. *Eur J Cardiovasc Nurs*. 2009;8(2):125–128. doi:10.1016/j.ejcnurse.2008.10.004
14. Kowalski R, Mahon P, Boylan G, McNamara B, Shorten G. Validity of the modified observer's assessment of alertness/sedation scale (MOAA/S) during low dose propofol sedation: 3AP6-3. *Eur J Anaesthesiol*. 2007;24:26–27. doi:10.1097/00003643-200706001-00097
15. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg*. 1970;49(6):924–934. doi:10.1213/00000539-197011000-00020
16. Vacharaksa K, Thongrakard T, Vacharaksa A. Needs of non-pharmacological management versus sedation or general anesthesia for dental treatment in older adults with special needs: a systematic review. *Health Policy*. 2025;154:105262. doi:10.1016/j.healthpol.2025.105262
17. Rex DK, Bhandari R, Lorch DG, Meyers M, Schippers F, Bernstein D. Safety and efficacy of remimazolam in high risk colonoscopy: a randomized trial. *Dig Liver Dis*. 2021;53(1):94–101. doi:10.1016/j.dld.2020.10.039
18. Henthorn KM, Dickinson C. The use of flumazenil after midazolam-induced conscious sedation. *Br Dent J*. 2010;209(11):E18. doi:10.1038/sj.bdj.2010.1132
19. Rosli MSA, Heidari E. Re-audit of the use of flumazenil following midazolam-induced conscious sedation. *BDJ Open*. 2023;9(1):36. doi:10.1038/s41405-023-00163-7
20. Conway A, Chang K, Mafeld S, Sutherland J. Midazolam for sedation before procedures in adults and children: a systematic review update. *Syst Rev*. 2021;10(1):69. doi:10.1186/s13643-021-01617-5
21. Kaplan K, Hunsberger HC. Benzodiazepine-induced anterograde amnesia: detrimental side effect to novel study tool. *Front Pharmacol*. 2023;14:1257030. doi:10.3389/fphar.2023.1257030
22. Zhao N, Zeng J, Fan L, et al. Moderate sedation by total intravenous remimazolam-alfentanil vs. propofol-alfentanil for third molar extraction: a prospective randomized controlled trial. *Front Med*. 2022;9:950564. doi:10.3389/fmed.2022.950564
23. Oue K, Oda A, Shimizu Y, et al. Efficacy and safety of remimazolam besilate for sedation in outpatients undergoing impacted third molar extraction: a prospective exploratory study. *BMC Oral Health*. 2023;23(1):774. doi:10.1186/s12903-023-03538-2
24. Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled Phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg*. 2012;115(2):284–296. doi:10.1213/ANE.0b013e318241f68a
25. Armfield JM, Stewart JF, Spencer AJ. The vicious cycle of dental fear: exploring the interplay between oral health, service utilization and dental fear. *BMC Oral Health*. 2007;7:1. doi:10.1186/1472-6831-7-1
26. De stefano R, Bruno A, Muscatello MR, et al. Fear and anxiety managing methods during dental treatments: a systematic review of recent data. *Minerva Stomatol*. 2019;68(6):317–331. doi:10.23736/S0026-4970.19.04288-2